ORIGINAL ARTICLE

Formulation and *In-vitro* Evaluation of Baclofen Transdermal Patches

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Abstract

Aim: The aim of this study is to formulate and evaluate of baclofen transdermal patches using different polymers, penetration enhancers, and plasticizers. A drug with different film forming polymers was subjected to compatibility study. In addition, *in-vitro* permeation across animal skin for the best formulation was investigated. **Materials and Methods:** After studying the incompatibility of baclofen and other polymers used, the pure drug baclofen was formulated as transdermal patches composed of different polymers by solvent evaporation method and the formulations were 16. Then, the physicochemical properties of formulated patches were evaluated to determine the best optimum formula to be examined *in-vitro* release. **Results and Discussion:** The drug excipient compatibility study revealed no interaction between baclofen and polymers used. All the physicochemical studies of formulated patches were satisfactory except the formulation. The best-chosen formula was F13 that composed of polyvinyl alcohol as film-forming polymer and Carbopol 940 as bioadhesive polymer with propylene glycol as plasticizer and dimethyl sulfoxide as penetration enhancer. **Conclusion:** Study indicates that baclofen can be formulated as transdermal patches of acceptable appearance and suitable drug release through 24 h.

Key words: Baclofen, compatibility study, *in-vitro* release, permeation enhancer, plasticizer, transdermal patch

INTRODUCTION

In current years, there is increased interest in advanced drug delivery systems as a new approach of administering drugs. From these approaches, a recent one delivers drug molecules into blood stream at sustained and predetermined rate using the skin as a site of application. Transdermal drug delivery systems are considered to be a type of new drug delivery systems that are established and approved by numerous scientific documents.[1] These systems, in comparison with traditional dosage forms, provide many advantages such as increasing systemic bioavailability of drugs, improving patient compliance in a chronic therapy, avoiding first-pass effect of liver, sustaining and controlling drug delivery, keeping a constant and extended drug level in circulation, reducing the frequency of drug administered, and prolonging the duration of drug in the body. Therefore, they lead to a maximum therapeutic action and minimum of side effects. They also maintain the drug concentration in the blood to be within the therapeutic index, thus, ensuring that they neither decrease under the minimum effective concentration nor increase above the minimum toxic concentration.[2,3]

A muscle spasm is defined as an involuntary contraction of muscles leading to intense pain, and the effective treatment might be as physical therapy, dietary changes, or intake medications that include agents called muscle relaxants which are drugs that work by decreasing the tone of skeletal muscle causing relaxation of muscle indicating to relieve skeletal muscle spasms and accompany pain.[4,5] Baclofen is an analog of the putative inhibitory neurotransmitter gamma amino butyric acid that belongs to the group of muscle relaxants and is primarily indicated for muscle spasms. The main site of action is the spinal cord where it inhibits polysynaptic and monosynaptic refluxes (no muscle weakness), and it

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also relieves spasticity that is related to many neurological disorders such as multiple sclerosis, spinal injuries, and flexor spasms.[6] Baclofen is absorbed orally in different ratios with a high value of distribution on the body, and it is available on market as an oral tablet as well as an intrathecal injection. It is excreted in urine and undergoes a first-pass metabolism in liver.[7] It has many pharmacokinetic disadvantages orally as it is absorbed in the upper portion of small intestines, it has a short biological half-life of 3-4 h which makes it short duration of action,[8,9] so it needs to be taken frequently that leads to patient incompliance. Due to all the previous limitations of oral baclofen, many studies designed to formulate oral dosage forms of sustained release but the results were unsuccessful due to many reasons such as dose dumping.[10,11] The physicochemical and pharmacokinetic data of baclofen that were collected from the best available sources make it as an excellent candidate for transdermal drug delivery system.[7,12-14] The dose of baclofen is 5 mg 3 times daily, increased to 10 mg 3 times daily for 3 days. The half-life of baclofen is 3-4 h which means that this short duration of action leads to extensive frequent dosing to maintain the nanogram therapeutic concentration.

The aim of this study was to formulate baclofen transdermal patches using different polymers, penetration enhancers, and plasticizers. Drug with different film forming polymers were subjected to compatibility study. In addition, *in-vitro* permeation across animal skin for the best formulation was investigated. The prepared patches were subjected to physical evaluations such as moisture content, drug content, *in-vitro* drug release, and kinetic analysis drug release data.

MATERIALS AND METHODS

Materials

Baclofen was kindly supplied as a gift from Alfath Group (PharoPharma, Egypt), hydroxypropyl methylcellulose (HPMC) was supplied as a gift from Yemeni-Egyptian Company, Sana'a, Yemen. Propylene glycol (PG) was kindly supplied by Pharmacare, Sana'a, Yemen, and polyvinyl alcohol (PVA) and Carbopol 940 (CP940) were purchased from Loba Chemie, Mumbai, India. Sodium alginate (SALG), oleic acid (OA), dimethyl sulfoxide (DMSO), and dibutyl phthalate (DBP) were purchased from Sigma Chemicals, Cairo, Egypt. Other chemicals were provided by UST laboratories. Water used in this study was distilled.

Compatibility study of baclofen with polymers

Fourier transform infrared analysis (FTIR) studies

FTIR data of dried samples of the pure baclofen, pure polymers, and their physical mixture were recorded in an FTIR spectrophotometer using the potassium bromide disc method.[15,16] Each sample was pulverized and intimately mixed with a dried powder of IR grade potassium bromide at a weight ratio of 1:100, then it was pressed using a hydrostatic press at a pressure of 10 tons for 5 min at room temperature. The result disc was placed in the sample holder and the spectra were recorded over the wave number ranges 4000-400/cm at a resolution of 4/cm. The peak location of the pure baclofen and the pure polymers were analyzed and compared with the spectra of their physical mixture.

Determination of λ_{max} wavelength of baclofen and calibration curve in phosphate buffer solution (pH 7.4)

In this study, baclofen was determined by ultraviolet (UV)-spectrophotometry. A small amount of baclofen was dissolved in phosphate buffer solution (pH 7.4) and scanned for wavelength from 200 to 400 nm on the UV spectrophotometer (Analytikjena, Germany) to determine the λ_{max}. Baclofen stock solution was then prepared by dissolving 70 mg of the drug in 60 ml of phosphate buffer solution (pH 7.4) and was filled up to 70 ml in a volumetric flask. This stock solution (1 mg/ml) was then diluted with phosphate buffer solution (pH 7.4) to obtain a series of solutions of 10-100 µg/ml. Then, from the prepared stock solution, aliquots of 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10 ml were separately diluted to 100 ml using the same buffer. The resulting solutions were equivalent to 10, 20, 40, 50, 60, 70, 80, 90, and 100 µg/ml, respectively. The absorbance of these solutions was measured spectrophotometrically at 268 nm, using phosphate buffer solution (pH 7.4) as a blank. The standard calibration curve was obtained. The absorbance of each sample was plotted against the corresponding concentrations, and the relation was found to comply with Beer' Lambert law. The equation for the best line fit was obtained and the procedural constant (k) was calculated.

Baclofen diffusion study using animal live skin

The baclofen permeation tests through the animal live skin were performed in a modified Franz diffusion cell.[17,18] The drug diffusion test was carried out using male rabbits in which the abdominal skin of rabbits (3.5 kg) was used after completing all the ethical needs including anesthesia with chloroform. The skin was carefully shaved using an electronic clipper, and a full-thickness skin (i.e., epidermis, subcutaneous, and dermis) was excised under esthetic effect. The subcutaneous fat with other blood vessels were removed and then stored at 4-5°C. The skin was rinsed with water for many times and then mounted between the two compartments of the diffusion cell. The receptor compartment was filled with 150 ml of phosphate buffer solution pH 7.4, and the donor compartment was filled with only 1 ml of baclofen solution 21 mg/ml. The diffusion cell with the fitted animal skin was kept inside a beaker containing receptor medium in which the temperature was maintained at 37 ± 0.5°C by putting it on a controlled hot plate. This whole assembly was kept on a container with a magnetic stirrer to provide continuous stirring during the whole experiment at a speed of 50 rpm.

The donor compartment was covered, and the samples of 2 ml were withdrawn (compensate later) at various time points and stored at room temperature until analysis. Permeation studies were carried out over 12 h, and samples were withdrawn at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12 h using needle syringes. The sample absorbance was read by a UV-spectrophotometer at 268 nm taking the phosphate buffer solution (pH 7.4) as a blank. The experiment was triplicated, and the mean result was recorded. The cumulative amount of baclofen permeated was calculated and then plotted against time. Different parameters (flux rate, permeability, diffusion coefficient, and lag time) were computed. The cumulative amount of baclofen permeated (Q_{12}) was also obtained for various formulae.[19,20]

Improvement of baclofen permeability

A solution of baclofen (21 mg/ml) was prepared in phosphate buffer solution (pH 7.4), and it was incorporated with a penetration enhancer to 1%, 3%, and 5% v/v concentration with OA and 0.5, 1 and 3% v/v concentration with DMSO.[21,22] The permeation study was performed as described previously.

Preparation of transdermal patches[23]

Preparation of baclofen transdermal patches containing HPMC as film-forming polymers

Baclofen was dissolved in 3 ml of distilled water containing 2.5% (v/v) of plasticizer with constant stirring. Then, a penetration enhancer in concentration 1% (v/v) was added. Subsequently, HPMC (1% w/v) was mixed with the weighed quantity of bioadhesive polymer 0.5% (either SALG or CP940). This homogenously mixture was gradually added to the solution of baclofen with continuous stirring. Finally, distilled water up to 10 ml was added. When the solution became completely hydrated, gel consistency was obtained, then the solution was subjected to sonication to remove any air bubble. The gel was casted into glass petri dish (6.2 cm diameter, 10 mm depth) and left overnight to be dried at room temperature. The dried patches were removed carefully, covered with an aluminum foil, and finally stored in desiccators for later evaluation tests. Dosage units were made by cutting each formulated patch into pieces, each of which contained 21 mg baclofen packed in an aluminum foil that were put in glass containers at room temperature to maintain their integrity, flexibility, and elasticity.

Preparation of baclofen transdermal patches containing PVA as film-forming polymers

PVA (3% w/v) was dissolved in two-thirds of the determined amount of hot distilled water (80-100°C) with constant stirring, then it was cooled. The mixture of baclofen, penetration enhancer, and plasticizer was added to the cooled PVA solution with continuous stirring. Then, the required amount of bioadhesive polymer was added with stirring, and the final volume was filled with distilled water to be 10 ml. Then, it was prepared as the same manner as previously mentioned in HPMC patches. Formulations are listed in Table 1.

Table 1: Composition of different transdermal patches using different polymers

Formulation code	Film forming polymer				Bioadhesive polymer				Plasticizer		Penetration enhancer	
	HPMC		PVA		SALG		CP940		PG (ml)	DBP (ml)	DMSO (ml)	OA (ml)
	mg	%	mg	%	mg	%	mg	%				
F1	100	1			50	0.5			0.25		0.1	
F2	100	1			50	0.5			0.25			0.1
F3	100	1			50	0.5				0.25	0.1	
F4	100	1			50	0.5				0.25		0.1
F5			300	3	50	0.5				0.25	0.1	
F6			300	3	50	0.5			0.25		0.1	
F7			300	3	50	0.5				0.25		0.1
F8			300	3	50	0.5			0.25			0.1
F9	100	1					50	0.5	0.25		0.1	
F10	100	1					50	0.5	0.25			0.1
F11	100	1					50	0.5		0.25	0.1	
F12	100	1					50	0.5		0.25		0.1
F13			300	3			50	0.5	0.25		0.1	
F14			300	3			50	0.5	0.25			0.1
F15			300	3			50	0.5		0.25	0.1	
F16			300	3			50	0.5		0.25		0.1

HPMC: Hydroxypropyl methyl cellulose, PVA: Polyvinyl alcohol, PG: Propylene glycol, DBP: Dibutyl phthalate, DMSO: Dimethyl sulfoxide, OA: Oleic acid, CP40: Carbopol 940, SALG: Sodium alginate

Evaluation of baclofen transdermal patches

The components of transdermal patches have profound effect on the physical and mechanical characteristics, the release and permeation of drugs. Therefore, the formulated patches were evaluated to choose the patches having the most satisfactory properties. Formulated-dried patches of 3.77 cm^2 area were examined for physical appearance, drug content uniformity, thickness, folding endurance, bioadhesion, moisture content, and *in-vitro* drug release tests.

Physical appearance

The formulated patches were evaluated and estimated by visual inspections for their physical appearances, including color, elegance, clarity, homogeneity, stickiness, texture, uniformity, smoothness, flexibility, transparency, or presence of air bubbles that play an important role in the patient compliance and acceptance, physical resistance during preparation, storing, and also therapeutic efficacy. Samples with air bubbles, cracks, precipitated, or heterogeneous surfaces were excluded from the analysis.[24,25]

Drug content uniformity

The baclofen transdermal patch units of each formulation of specified area (3.77 cm^2) were weighed accurately, and then placed in a volumetric flask filled with 250 ml of phosphate buffer solution (pH 7.4) and continuously stirred by a magnetic stirrer. The solution was then filtered and diluted with the same medium suitably, if required. The amount of baclofen was determined by UV spectrophotometer at λ_{max} 268 nm. The average of three patches readings was taken and the baclofen concentrations were calculated from a standard calibration curve using Microsoft Excel and expressed as percentages.[17,26]

Folding endurance

It was counted manually for different prepared patches in which three patches of each formula with size (1 cm × 2 cm) were cut using a sharp blade. The folding endurance of films was measured by frequently folding a strip at the same point till it is broken or folding up to 200 times at one point breaking which gave folding endurance of film.[27]

Bioadhesion test

Stainless steel ball was moved on smooth surface of inclined track so that it rolled down and came into contact with the surface of adhesive that resists this movement. The distance the ball travelled on the adhesive gave the value of tack, which is expressed in centimeters. The test was performed at least 5 times and the average was calculated. The tested strip used in this study must be fresh, and the rolling ball must be cleaned after each procedure. Since the formulated patches were dried, the adhesive would be reduced from being fresh. Therefore, to resolve this problem, a thick "soft" backing or a thick layer of adhesive was coated into each tested patches.[28,29]

Percentage moisture content

Three patches from each formulation (3.77 cm^2) were weighed by an electronic balance and the mean value was calculated, and this was an initial weight. Then, the weighed patches were placed in a desiccator containing an anhydrous calcium chloride powder at normal room temperature for 24 h. Then, after 24 h, the patches were weighed again, and the final weight was noted. The percentage of moisture lost was calculated according to equation (1):[30,31]

$$\% \text{ Moisture content} = [(\text{Initial weight} - \text{Final weight})/\text{Final weight}] \times 100 \quad (1)$$

Percentage moisture absorption

The films were placed in a desiccator of potassium chloride solution for 24 h. Then, after 24 h when the change in weight stopped, the final weight was noted. The percentage of moisture uptake was calculated and determined using equation (2):[28,31]

$$\% \text{ Moisture absorption} = [(\text{Final weight} - \text{Initial weight})/\text{Initial weight}] \times 100 \quad (2)$$

In-vitro drug release studies[32,33]

The paddle over disc method (USP apparatus V) may be used to measure the release rate of the drug from the formulated transdermal patches. Dry transdermal patches of surface area (3.7 cm^2) of the defined shape and thickness were fixed over a circular glass plate (diameter 5 cm) with a glue to fix them. The patch fixed with glass plate was located at the bottom of the dissolution vessel filled with a 250 ml of the dissolution medium of phosphate buffer solution (pH 7.4). Only one side of the patch was exposed to the dissolution medium, and the apparatus was operated at temperature of 32 ± 0.5°C and speed of 50 rpm. The samples of 5 ml were withdrawn at predetermined time intervals up to 12 h and compensated with fresh diffusion medium. Then, these samples were analyzed by a UV spectrophotometer at λ_{max} 268 nm after filtration and dilution, if required. The test was performed in triplicate, the mean values were reported, and the cumulative percent released was calculated and plotted versus time.

Study of release mechanisms

To determine the release mechanism of baclofen from the formulated transdermal patches, the data for the first 70% of

the released drug were plotted using Peppas and Korsmeyer equation (3):[16,34,35]

$$M_t/M_\infty = k \cdot t^n \quad (3)$$

Where, M_t/M_∞ is the fraction of baclofen (%) released at time t (h), n is a diffusional exponent, which characterizes the type of release mechanism and k is the apparent constant of release rate (%/h) considering the structural and geometrical characteristics of the transdermal patches.

RESULTS AND DISCUSSION

Compatibility study of baclofen with polymers

FTIR analysis studies

The compatibility of baclofen with the selected polymers was confirmed by FTIR spectroscopy. Samples of pure baclofen with or without the selected polymers were scanned in the region of a wave number ranges 4000-400/cm.[36] The scans were examined for the presence of drug fingerprint, shifting, appearing, and masking of drug peaks by the presence of polymer in the formulation. The FTIR spectra of pure baclofen were observed in Figure 1a. The FTIR spectrum of baclofen exhibited the characteristic absorption peaks at 3300/cm (N-H_2 stretching), 2984.542/cm (aromatic C-H stretching), broad peak at 2598.642/cm extended up to 3100/cm (O-H of alcohol and carboxylic acid stretching), 2155.047/cm (alkynyl C≡C stretching), 1922.494/cm (carboxylic acid C=O stretching), 1626.875/cm (alkenyl C=C stretching), 1531.447/cm (aromatic C=C bending), and the peaks which were appeared at regions <1500 cm^{-1} including 1401.322/cm (O-H bending), 1245.755/cm (C-O stretching), 834.388/cm (C-Cl stretching) and 700-800/cm (benzene), and considered as fingerprints for baclofen. These data are in good agreement with those reported in literature for baclofen.[37]

Figure 1 represents comparative FTIR spectra of pure baclofen and its freshly prepared physical mixtures with different polymers selected for the study. The IR spectra of these mixtures showed the absorption bands, indicating the presence of drug and polymer. It was observed that all bands of baclofen were maintained at the same positions in FTIR spectra of baclofen blends with HPMC, SALG, CP940, PVA, and polyvinylpyrrolidone K-25 which means that no possible interaction between baclofen and the studied polymers. Since the main peaks of drug-polymer mixture were approximately the same as the peaks of pure drug. In the present study, it has been noted that there are no distinctive physical or chemical interactions between the drug and the polymers. Thus, FTIR analysis results propose that the baclofen and polymers used are compatible.

Determination of maximum wavelength of baclofen and calibration curve in phosphate buffer solution (pH 7.4)

The UV scanning of baclofen in phosphate buffer solution (pH 7.4) revealed a maximum at λ_{max} 268 nm as shown in Figure 2. Figure 3 shows that a linear relationship between the absorbance at the specified λ_{max} and the corresponding concentrations obtained within the range 10-100 µg/ml. The slope was determined and the procedural constant (k) was calculated from the 1/slope which was equal to 101.1. Linearity is demonstrated by R^2 value of 0.9993.

Baclofen permeability test using animal skin

In-vitro diffusion study is considered to be a prediction step to determine *in-vivo* performance of a transdermal patch. The quantity of drug permeated in each time interval for baclofen solution was calculated and their cumulative amounts were obtained. The cumulative amounts of baclofen diffusing per unit skin area (Q) were plotted versus time as shown in Figure 4, and by knowing the slope of the linear portion, the steady state flux was obtained. The permeability coefficient (Kp) then was computed, and the lag time (t_{lag}) was estimated by the extrapolation of the linear part of the plot to the time axis. From the lag time and thickness of skin, the diffusion coefficient was obtained and the cumulative amount of drug permeated at the end of the test (Q_{12}) was calculated. The permeation of baclofen across isolated human cadaver skin has been studied. Moreover, the flux reported was 0.18 ± 0.08 µg cm^{-2} h^{-1} in aqueous solutions, and it was very poor.[38] The flux of baclofen across skin was 167.37 µg cm^{-2} h^{-1} with time lag 1.15 h. The permeability coefficient was 1.196 cm h^{-1} and diffusion coefficient was 3.76×10^{-5} mg h^{-1}. The cumulative amount of drug permeated after 12 h (Q_{12}) was 2193 µg cm^{-2}. The low diffusion coefficient of zwitterionic drug played an important role in this low flux through skin. The results obtained for the permeation of baclofen through the animal live skin represented that the baclofen has quite acceptable permeation characteristics. Therefore, the further increment in flux was made using various skin penetration enhancers to decrease the area of this system.

To increase the skin flux, two penetration enhancers: DMSO and OA were incorporated into formula and then estimated. The permeation profile of baclofen with skin penetration enhancers is presented in Figures 5 and 6. The results obtained clearly showed that the flux of baclofen is improved using penetration enhancers.

Permeation kinetic parameters of baclofen through animal live skin as a pure solution and using OA and DMSO as penetration enhancers on different concentrations are shown in Table 2. By calculating the enhancement ratio (ER), it was observed that the highest enhancement was with DMSO 1% and the slowest

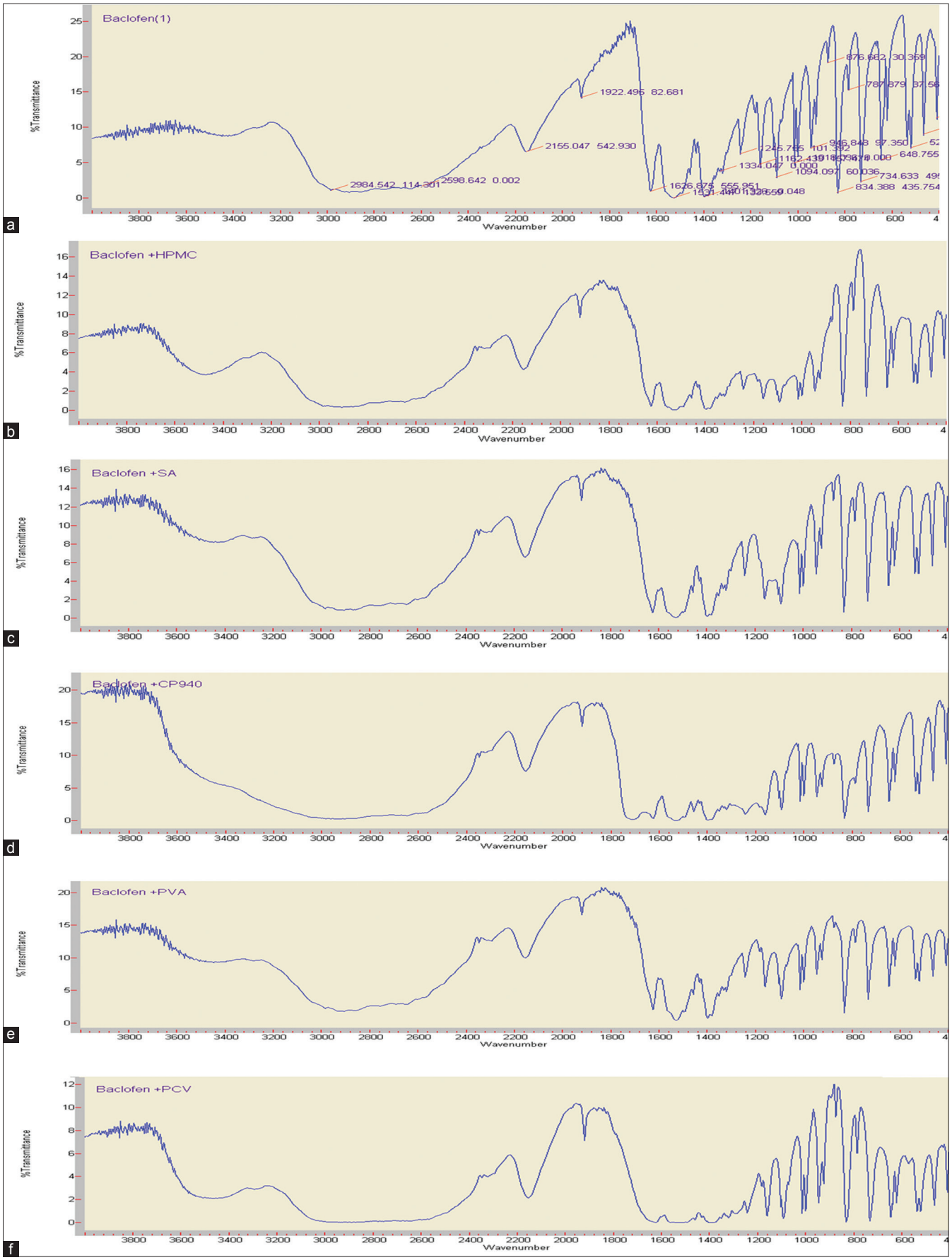

Figure 1: Fourier transform infrared analysis spectra for baclofen, (a) baclofen-hydroxypropyl methyl cellulose, (b) baclofen-sodium alginate, (c) baclofen-carbopol 940, (d) baclofen-polyvinyl alcohol, (e) and baclofen-polyvinylpyrrolidone K-25, (f) physical mixtures

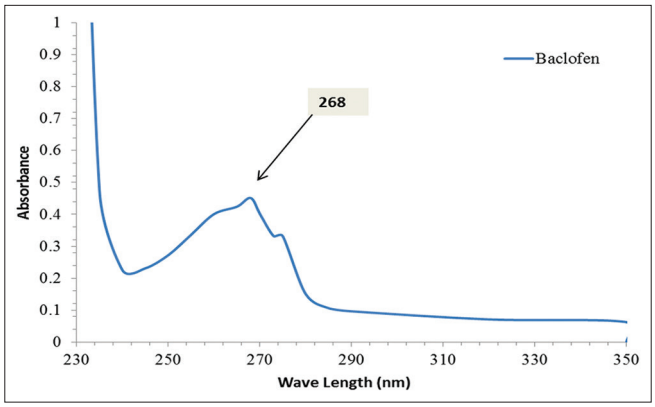

Figure 2: Ultraviolet absorbance spectrum of baclofen

was with using DMSO 0.5%. According to the flux values, the rank order for different mixtures was DMSO (1%) > OA (5%) > DMSO (3%) > OA (3%) > OA (1%) > DMSO (0.5%). It was found to be 374.73, 255.95, 239.10, 237.43, 199.50, and 162.63 µg cm^{-2} h^{-1}, respectively. According to the ER values of different concentrations, the selected penetration enhancers were the DMSO of 1% and OA on concentration of 1%. The using of OA in concentration of 5% gave ER 2.5, but the solution was highly oily that may lead to make patches disagreeable to patient and may effect on storage later. On the other way, using OA in concentration of 3% gave enhancement less than using 1% (1.91 and 1.89, respectively). In the case of DMSO, the best concentration was 1% with ER 4.11, whereas 3% gave low ER of 2.09 that may be due to micelles formation. It also

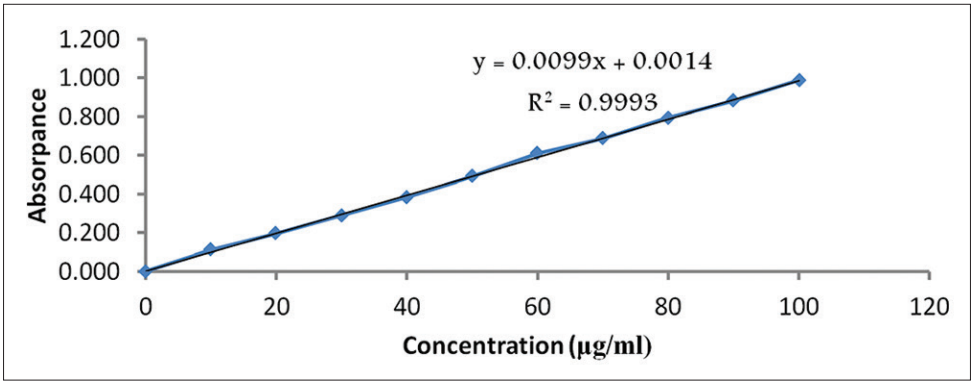

Figure 3: Calibration curve of baclofen in phosphate buffer solution (pH 7.4) using a ultraviolet spectrophotometer at λ_{max} 268 nm

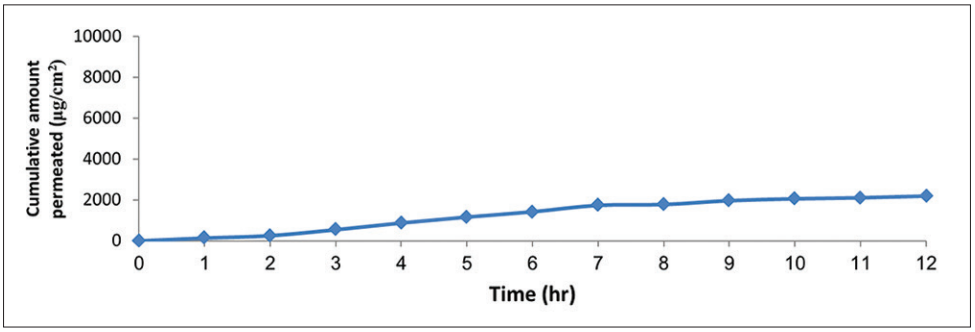

Figure 4: Permeation study of baclofen in phosphate buffer solution (pH 7.4) through rabbit live skin

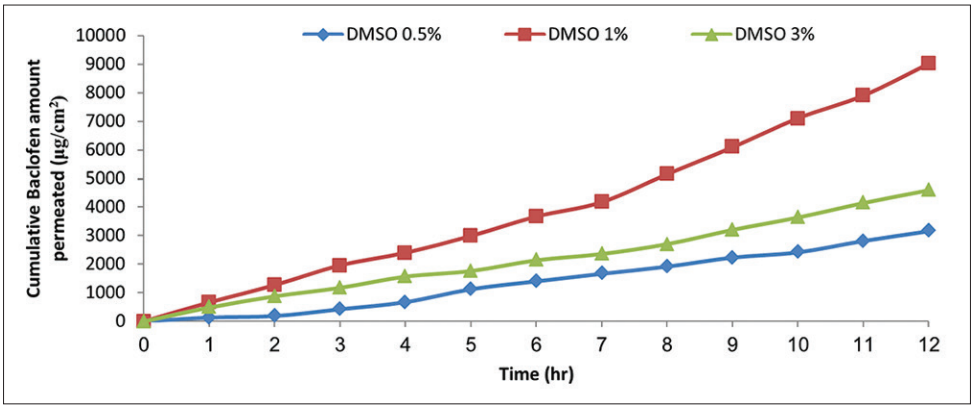

Figure 5: Permeation study of baclofen across animal live skin incorporated dimethyl sulfoxide as a penetration enhancer on different concentration

observed that the lag time was shortened when using OA and prolonged when using DMSO. Accordingly, the highest and most suitable concentrations for optimum penetration were 1% of OA and 1% DMSO. Results are shown in Table 2.

Evaluation of the prepared baclofen patches

Transdermal patches were formulated by the solvent evaporation method using various polymers to achieve a sustained and controlled release. Polymers were dissolved in the chosen solvent producing a clear viscous solution that results in obtaining a good film.

Physical appearance

The formulated patches were firstly and visually inspected for many characteristics such as homogeneity, flexibility, presence of air bubbles, color, and transparency. It was observed that all the formulae meet the ideal properties of the patches' physical appearances of except the formulae F7, F12, and F16 that are not correspond to these properties. The medicated patches had the same properties and appearances except the transparency in which the patches were opaque because of the white color of baclofen due to the uniform dispersion of the large amount of baclofen powder. Therefore, it was concluded that according to physical appearance, only 13 formulae were appeared physically acceptable to complete the other physical characterizations and only three formulae were excluded.

The physicochemical properties of the prepared patches were obtained and represented in Table 3. Using the electronic digital micrometer, the thickness of patch was determined, and the mean value was recorded.

The obtained results showed no much difference in thickness within the same formulation (film thickness variation was <5%), but there were differences between variously composed formulations and this due to the amount of polymers and differences in lipophilicity of each polymer. The thickness in various formulations was at the range of 442.167 ± 2.787 µm to 121.333 ± 1.211 µm. The highest values of thickness were with F6, while the lowest were with F1. The results of thickness showed a low standard deviation (SD) that ensures

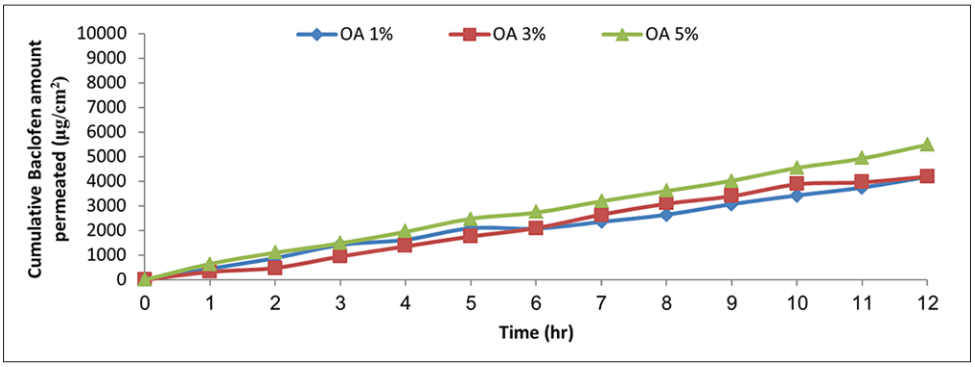

Figure 6: Permeation study of baclofen across animal live skin incorporated oleic acid as a penetration enhancer on different concentration

Table 2: Permeation kinetic parameters of baclofen through animal live skin

Solution composition	SSF (µg cm^{-2} h^{-1})	Q_{12} (µg cm^{-2})	t_{lag} h	Permeability coefficient (cm h^{-1})	ER	Diffusion coefficient×10^{-5} (cm^2 h^{-1})	r^{2*}
Baclofen solution	167.37	2193	1.15	1.196	-	3.76	0.9800
Baclofen with OA 1%	199.50	4187	0.35	1.425	1.91	1.14	0.9936
Baclofen with OA 3%	237.43	4139	0.75	1.696	1.89	2.45	0.9959
Baclofen with OA 5%	255.95	5489	0.20	1.828	2.50	0.65	0.9989
Baclofen with DMSO 0.5%	162.63	3155	1.45	1.162	1.44	4.74	0.9941
Baclofen with DMSO 1%	374.73	9018	1.5	2.677	4.11	4.90	0.9928
Baclofen with DMSO 3%	239.10	4588	1.8	1.708	2.09	5.88	0.9957

SSF: Steady State Flux, DMSO: Dimethyl sulfoxide, OA: Oleic acid, ER: Enhancement ratio

the uniform distribution of the drug and polymer over petri dish surface.

The results obtained from the flatness test showed no variations in the strip lengths that ensure smooth surfaces of patches. The baclofen loaded patches were evaluated for weight uniformity, and the results were observed uniform. The weights were ranged from 38.20 ± 1.47 mg to 74.63 ± 2.18 mg. The patches' weight variation was <5% in each formula, and this was found to be uniform among different patches. The variations in weight may be due to the variation in density of different combinations of polymers and also due to the result of difference in the molecular weight and proportion of the excipients used in the patches. It may also be due to the moisture percentage in each formula. The allowed limit for the deviation less than mg is ±10%. Accordingly, all the formulated patches were within the limit. Therefore, baclofen was distributed with an acceptable allowed deviation.

The average drug content of prepared medicated patches was found containing between 93.80 ± 0.85% (F13) and 104.30 ± 0.79% (F15) of the labeled amounts of baclofen per patch as presented in Table 3. The mean percentage deviation was observed to be allowed, and the patches were so officially acceptable for content uniformity. From the data obtained, it was observed that the distribution of baclofen throughout the patches was acceptable regardless of the polymer type and proportions. Low values of SD in the drug content and previous tests data reflected that there was no significance difference within each batch. The flexibility of patches that required to be easily handling could be known by their folding endurance which was measured manually. The results were optimum for all formulae with more satisfactory with F9 and F13, and the patches exhibited suitable physical and mechanical characteristics as shown in Table 3. From this test, it was noticed that all patches were flexible and gave resistance to breakage upon folding them for more than 200 times at the same point and showed no cracks which were taken as an end point. Moreover, it was noticed that there was low flexibility on formulae composed of PVA as compared to HPMC. This might be due to the high concentration of PVA as the polymer amount decreased the folding endurance and the patch became more friable. The estimation of bioadhesion of patches was very essential to maintain the contact with the skin for a large period to improve the sustaining effect of the drug. According to Table 3, it was observed that the highest bioadhesion force was when using PVA as a film forming polymer and SA as a bioadhesive polymer represented in F5, F6, and F8, which were 6.84 ± 0.59 cm, 4.55 ± 0.40 cm, and 8.82 ± 0.96 cm, respectively. The results showed that the patches containing HPMC as a film forming polymer and SA as a bioadhesive polymer were with low bioadhesion force that was ranged from 19.40 ± 2.191 cm to 31.70 ± 2.049 cm in F2 and F3, respectively. The results of moisture content were calculated and showed in Figure 7. The moisture content was observed to be a moderate level from 0.00 ± 0.000 to 78.23 ± 0.699%. The results obtained were related to a plasticizer as the increase in case of PG (F1 and F13 as examples) and the decrease in case of DBP (F3 and F4 showed no moisture content). On the other hand, the results of the moisture absorption tests are shown in Figure 8 found to be low compared to the moisture loss and ranged from 0.00 ± 0.000 (F1, F3, and F4) to 37.2 ± 0.498% (F13).

In-vitro drug release studies

The dissolution study is an easy method to characterize delivery systems and evaluate the effect of excipients on the rate of drug release. In this study, the dissolution studies were performed for 12 h. The *in-vitro* release profiles of baclofen from transdermal patches containing 1% HPMC as a film forming polymer are shown in Figure 9, 3% PVA as a film

Table 3: Physicochemical characterizations of various transdermal patches

Formulation code	Drug content (%)	Folding endurance	Moisture content (%)	Moisture uptake (%)	Bioadhesion (cm)
F1	100.63±0.81	More than 200	68.41±0.482	0.0±0.000	29.10±2.408
F2	98.93±0.90	More than 200	13.41±0.761	6.2±0.478	19.40±2.191
F3	95.10±0.46	More than 200	0.00±0.000	0.0±0.000	31.70±2.049
F4	100.60±0.79	More than 200	0.00±0.000	0.0±0.000	28.00±2.550
F5	99.70±0.66	More than 200	2.72±0.375	1.6±0.219	6.84±0.590
F6	101.43±0.74	More than 200	55.45±0.542	12.3±0.555	4.55±0.406
F8	100.17±0.35	More than 200	12.01±0.638	12.7±0.032	8.82±0.968
F9	101.70±0.46	More than 200	82.50±0.174	3.4±0.175	15.86±1.633
F10	99.13±0.81	More than 200	26.44±0.475	14.8±0.452	17.60±2.074
F11	101.03±0.25	More than 200	7.38±0.508	18.8±10.941	23.40±1.673
F13	93.80±0.85	More than 200	78.23±0.699	37.2±0.498	11.58±1.069
F14	99.00±0.98	More than 200	16.77±0.182	17.8±0.106	13.44±1.212
F15	104.30±0.79	More than 200	1.78±0.285	4.6±0.484	10.62±1.154

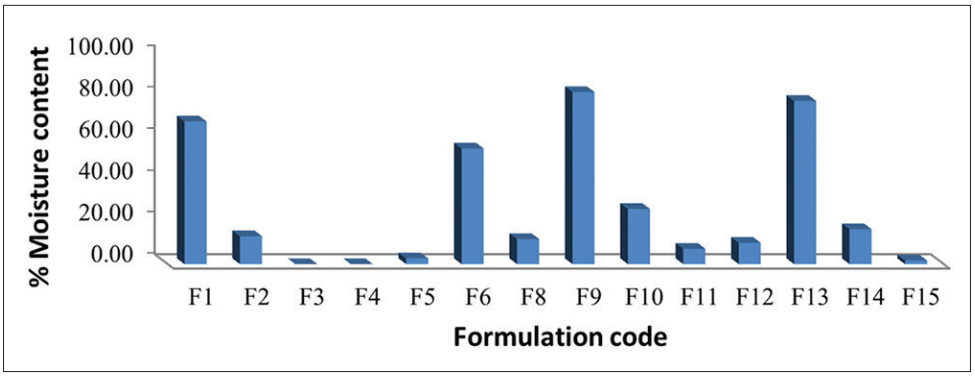

Figure 7: Percentage of moisture content for different formulated baclofen transdermal patches

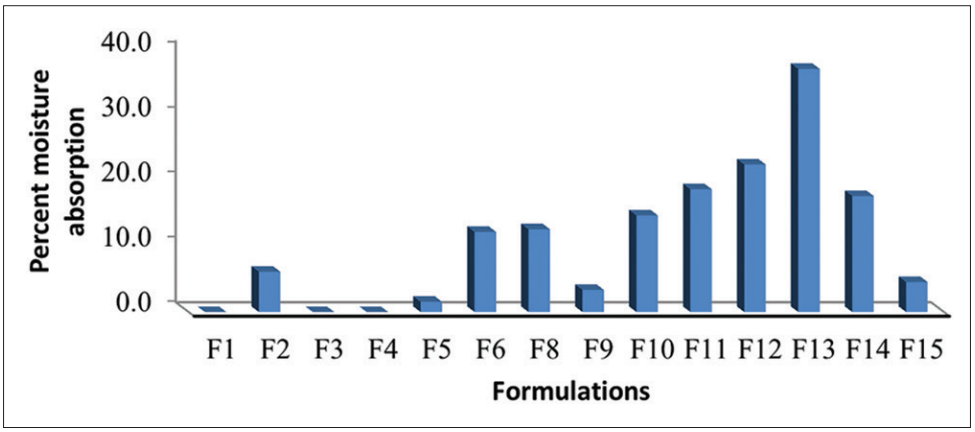

Figure 8: Percentage of moisture absorption for different formulated baclofen transdermal patches

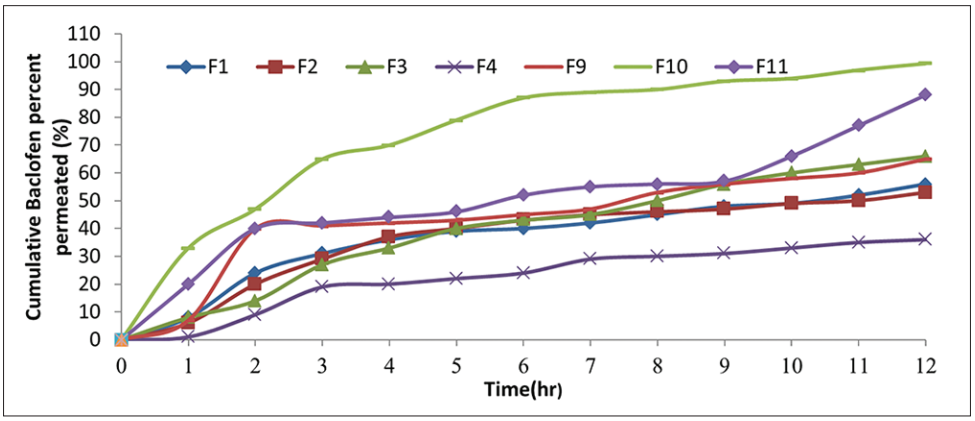

Figure 9: Release profiles of baclofen transdermal patches containing hydroxypropyl methyl cellulose as a film-forming polymer

forming polymerin [Figure 10], 0.5% SALG as a bioadhesive polymerin [Figure 11], and CP940 polymerin [Figure 12]. The effects of DMSO and OA as penetration enhancers on release are presented in Figures 13 and 14. It is observed from the plots that the drug release could be sustained and controlled depending on the type and proportion of polymers. It is also seen that the rate of drug release could be modified in a predictable manner by varying the type of penetration enhancers which had a clear effect in the rate of permeation.

In general, baclofen release was slower from films containing HPMC than films containing PVA which may be due to the high viscosity of HPMC compared to that highly hydrolyzed PVA.[39] The most slowest formulae were F4 and F2 when using HPMC and F14 and F13 when using PVA as film forming polymers. It can be seen that using HPMC as a film forming polymer and SALG as a bioadhesive polymer comparatively and largely reduced the drug release, whereas the patches containing PVA as a film forming polymer and SALG as a bioadhesive polymer showed a low decrease in drug release. It was noticed that the slowest release was obtained from patches containing OA as a penetration enhancer than DMSO as shown in Figures 13 and 14. This might be returned to the large hydrophobicity, and the consequent lower dissolution

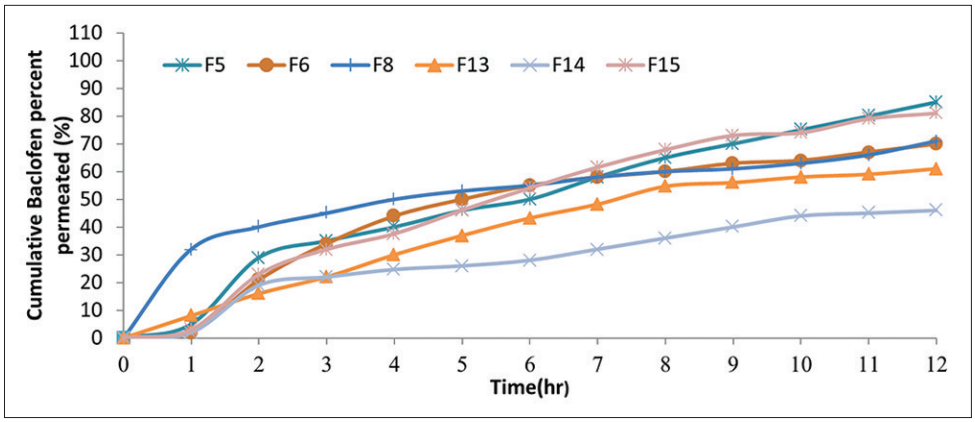

Figure 10: Release profiles of baclofen transdermal patches containing polyvinyl alcohol as a film-forming polymer

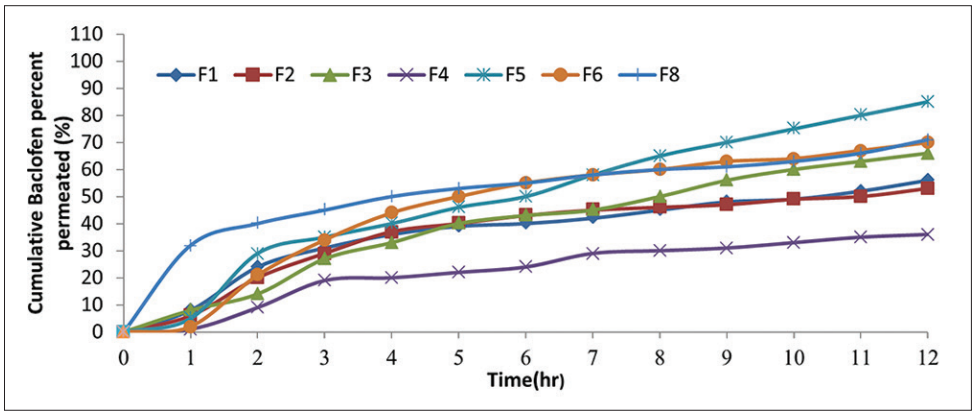

Figure 11: Release profiles of baclofen transdermal patches containing sodium alginate as a bioadhesive polymer

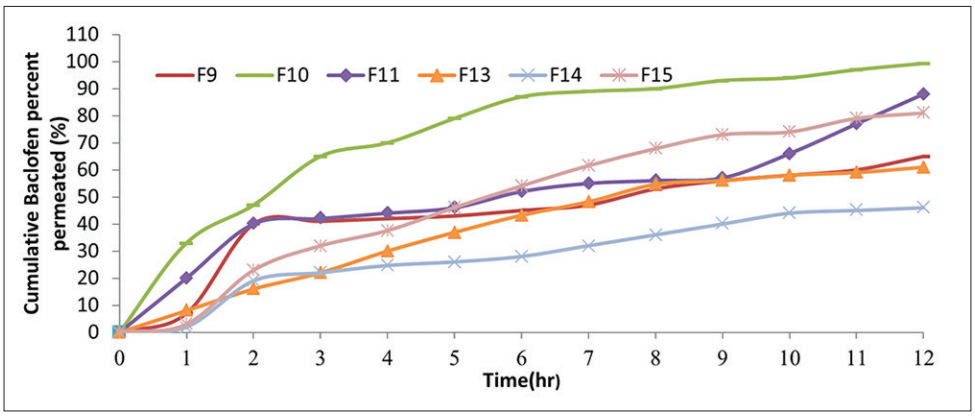

Figure 12: Release profiles of baclofen transdermal patches containing carbopol 940 as a bioadhesive polymer

and slower erosion of OA transdermal films, which prevented free and deep water penetration into the film.[40] The transdermal patch containing drug, HPMC, SALG, and OA (F2 and F4) and PVA, CP940 (F13 and F14) showed minimum *in-vitro* drug release, only 36% and 52% drug release were achieved in 12 h with T50% of 9.8 h and 17.4 h (in F4 and F2, respectively), and 46% and 61% with T50% of 13.2 h and 6.3 h (in F14 and F13, respectively). Regarding the formulation of sustained release, the minimum 60% of drug release over a 12 h period was desired for the purpose of this study for transdermal delivery. On the one hand, for formulations F2, F4, F13, and F14, it was evident that while the drug release was being controlled, approximately 36-61% of baclofen was only released from the patch at the end of 12 h. On the other hand, the data clearly showed that the baclofen release percentage was maximum (99-88%) for formulations containing HPMC film forming polymers (F10 and F11) and (85-81%) for formulations containing PVA film forming polymers (F5 and F15), respectively. In the case of formulations, F3 (T50% = 6.3 h), F6 (T50% = 5.6 h), F9 (T50% = 7.3 h), and F13 (T50% = 6.3 h) baclofen release was relatively fast and ranged between 60% and 70%.

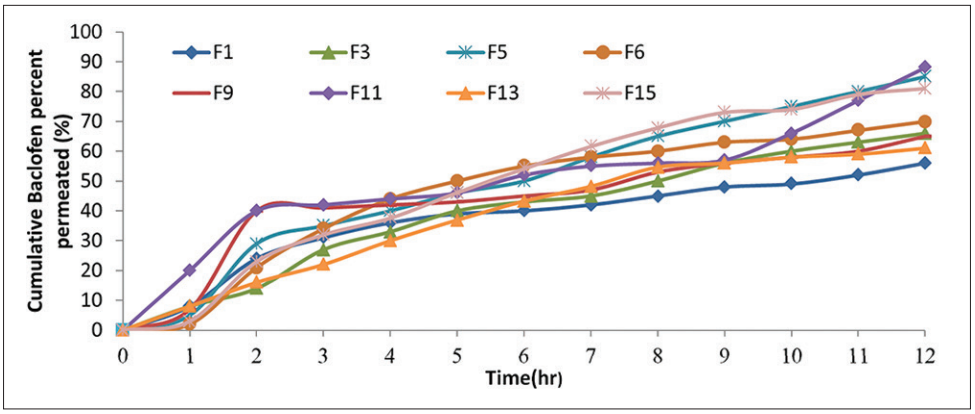

Figure 13: Release profiles of baclofen transdermal patches containing dimethyl sulfoxide as a penetration enhancer

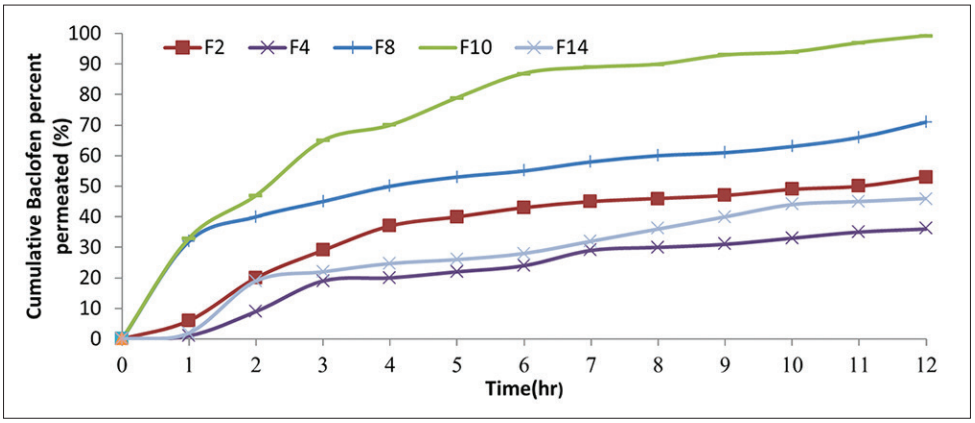

Figure 14: Release profiles of baclofen transdermal patches containing oleic acid as a penetration enhancer

Perhaps, this range of release could be more convenient for transdermal delivery. Thus, formulations which have released out of this range would not be considered appropriate for a controlled drug release profile.[16] The optimum formulations were acceptable when their baclofen release was 60-70% at the 12th h of dissolution, while the controlled release profile was still maintained throughout the study.

Kinetic analysis of baclofen released from different patches

Most satisfactory physicochemical patches were exposed to *in-vitro* dissolution studies, and corresponding results are shown in Figures 9-14. Baclofen release from patches was sustained and controlled over 12 h. To know the mechanism of this release, it had been tried by applying various kinetic models.[41] Analysis of the release data as zero-order and first-order kinetic models is shown in Table 4. The correlation coefficient (r^2) values were higher in the case of zero-order kinetic model than in the case of first-order kinetic model indicating that the drug release from the formulated patches followed zero-order kinetics. The correlation coefficients (r^2) were found to be in the range of 0.877-0.981 for zero order and 0.616-0.818 for first order. Plots of percent release versus time (Higuchi plots) were found to be linear with r^2 values >0.950 in all the cases indicating diffusion as the release mechanism from all the patches. Drug release parameters of the polymeric patches are summarized in Table 4.

To know more accurately the effect of the polymeric mixture on the release of baclofen, the results must be analyzed regarding to the semiempirical Korsmeyer-Peppas equation.[34,35,41] The data analyzed of K, n, and r^2 of this study baclofen release from the transdermal films are shown in Table 4. The values of n were in the range of 0.45 and 0.89 for all formulations except for F8, indicating anomalous (non-Fickian) release kinetics. Variations in the mechanisms of drug release from all the patches were observed. These variations were dependent on the composition or factors involved in the formulation.

CONCLUSION

Baclofen was selected successfully to be the candidate for the transdermal patch due to its physical and chemical properties that are corresponding to ideal transdermal patches. The theoretical release profile of baclofen from sustained layer was calculated to be a 21 mg daily dose as a maintenance dose. The physical appearance of different patches was acceptable except F7, F12, and F16 which were excluded due to the cracks. The most accepted physicochemical characterized patches were F2, F3, F4, F6, F9, F13, and F14

Table 4: Kinetic analysis of baclofen released from different patches

Formulation code	Correlation coefficient (r^2) *r*			Korsmeyer-Peppas model			
	Zero order equation	First order equation	Higuchi model	*K*	*n*	$t_{50\%}$ (h)	r^2
F1	0.931	0.735	0.984	0.1813	0.452	11.0	0.985
F2	0.913	0.748	0.973	0.1862	0.458	9.8	0.974
F3	0.981	0.810	0.985	0.1903	0.535	6.3	0.989
F4	0.955	0.800	0.975	0.1294	0.475	17.4	0.973
F5	0.980	0.793	0.983	0.1963	0.601	5.0	0.991
F6	0.933	0.771	0.971	0.1846	0.580	5.6	0.973
F8	0.877	0.616	0.974	0.1869	0.320	6.8	0.997
F9	0.887	0.704	0.952	0.2111	0.451	7.3	0.955
F10	0.893	0.646	0.979	0.1734	0.673	2.5	0.952
F11	0.940	0.694	0.966	0.1869	0.461	8.3	0.966
F13	0.973	0.811	0.982	0.1895	0.527	6.3	0.986
F14	0.964	0.791	0.977	0.1547	0.453	13.2	0.975
F15	0.976	0.808	0.980	0.1965	0.618	4.7	0.990

Time for 50% drug release ($t_{50\%}$ (h))

that were optimum to meet the ideal properties of transdermal patches. By studying the *in-vitro* release, F2 and F4 were the most satisfactory sustained release when using HPMC as a film forming polymer and F13 and F14 when using PVA as a film forming polymer. According to the analysis and comparing of all previous results, it was concluded that the best formulation was with F13 in which met the most satisfactory characteristics of the ideal transdermal patches. It gave good physical properties by appearing as translucent and flexible films. It was observed that F13 contained PG as plasticizers that gave more flexibility than those using DBP. In addition, it contained DMSO as penetration enhancer that was most penetrant than OA. Finally, it was noticed that F13 released baclofen slowly enough to be sustained released through 24 h to be taken once daily. Further *in-vivo* and stability studies were recommended for the best formula.

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